UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/901,612	07/28/97	FRANK B	HYZ-041FWC

HM12/0601

DIKE, BRONSTEIN, ROBERTS & CUSHMAN
EDWARDS & ANGELL
P.O. BOX 9169
BOSTON MA 02209

EXAMINER	
LARSON, T	
ART UNIT	**PAPER NUMBER**
1635	39

DATE MAILED: 06/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/901,612	Applicant(s) FRANK ET AL.	
	Examiner Thomas G. Larson, Ph.D.	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-20,36,40-50 and 207-224* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-20,36,40-50 and 207-224* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

1. The following action is responsive to Applicant's request for reconsideration in the paper filed 3/21/01 with a certificate of mailing dated 3/19/01.

2. The rejection of claims 1, 40-46, and 50 under 35 USC 102(e) as anticipated by Korba et al. is withdrawn in view of applicant's amendment to the claims filed 3/21/01.

3. The following rejections are either of record in the Office action mailed 10/23/00, or are new, but are necessitated by applicant's amendment to the claims, filed 3/21/00.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 17, 19, and 40-44 stand rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al. (cited in the Office action mailed 5/28/96) or Wu et al. (designated B4 on the PTO-1449 submitted with the information disclosure statement filed 8/24/95) for the reasons of record in the Office action mailed 5/28/96.

Claims 1, 17, and 19 are drawn to oligonucleotides comprising SEQ. ID. NOS: 16 and 18. Claims 40-44 limit the oligonucleotide of claim 1 to being a phosphorothioate-modified oligodeoxyribonucleotide.

Both Wu et al. documents disclose an oligonucleotide targeted to nucleotides 1903-1923 of the HBV genome (Wu et al. (J. Biol. Chem.) p. 12436, col. 2, 2nd full ¶, lns. 11-15; Wu et al. (WO 93/04701), p. 10, ln. 8). This oligonucleotide comprises both SEQ. ID. NO: 16 (comprises nucleotides 1903-1922, see specification, Table 1) and SEQ. ID. NO: 18 (comprises nucleotides 1910-1921, see specification, Table 1). The oligonucleotide taught by Wu et al is a phosphorothioate-modified oligodeoxyribonucleotide (Wu et al. J. Biol. Chem, p. 12436, col. 2, "Material and Methods" section, lns. 15-20, and Wu et al., WO 93/04701, p. 12, lns. 1-5).

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 8-14 , 36, 48, and 49 stand rejected and claims 40-46 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korba et al. (US Patent No. 5,646,262) for the reasons set forth in the office action mailed 10/23/00.

Claims 1, 8-14 , 36, 48, and 49 stand rejected for the reasons of record in the Office action mailed 10/23/00. Claim 1 has now been amended to recite an oligonucleotide comprising a sequence selected from the group consisting of SEQ. ID. NO: 7-19 and 45. As set forth in the previous Office action, oligonucleotides comprising SEQ. ID. NOS: 7-13 and 45 would be obvious in view of Korba et al.

Regarding claims 40-46, and 50, claims 44-46 limit the oligonucleotide of claim 1 to being modified, to comprising one or more phosphorothioate internucleoside linkages, to comprising ribonucleotides and/or deoxyribonucleotides. Claim 50 is drawn to a composition comprising the antisense oligonucleotide of claim 1 and a pharmaceutically acceptable carrier. Korba teaches that the anti-HBV oligonucleotides may be base on ribonucleotides or deoxyribonucleotides . Korba et al. further teach that the oligonucleotides may be modified and discloses phosphodiester, phosphorothioate or methylphosphonate linkages as examples of modifications (col. 6, ln. 61, - col. 7, ln. 13). Korba et al. also teach compositions comprising oligonucleotides and pharmaceutically acceptable carriers (col. 9, ln. 1, - col. 10, ln. 46).

Applicant's arguments filed 3/21/01 have been fully considered but they are not persuasive. The rejection is traversed on the grounds that the oligonucleotides taught by Korba et al. are targeted to a smaller portion of the HBV genome that those disclosed by applicant, and that many of the oligonucleotides disclosed by Korba et al. had little or no activity.

In response to the argument that the oligonucleotides taught by Korba et al. are targeted to a smaller portion of the HBV genome that those disclosed by applicant, the rejection made clear that it is the portion of the subject matter encompassed by oligonucleotides comprising applicant's SEQ. ID. NOS: 7-13 and 45 that is subject to this rejection. The portion of the HBV genome spanned by these sequences is encompassed by the oligonucleotides disclosed by Korba et al. Therefore, the arguments regarding the portions of the HBV genome targeted by applicant's SEQ. ID. NOS: 14-19 are irrelevant to this rejection.

Regarding the argument that many of the oligonucleotides disclosed by Korba et al. had little or no activity, Table 1 disclosed by Korba et al. shows that all of the L1-L3e antisense oligonucleotides targeted to the epsilon region of HBV (SEQ. ID. NOS: 39-56) had antiviral activity, as judged by the inhibition of viral DNA levels. Furthermore, Table 1 disclosed by Korba et al. shows that the oligonucleotides targeted to the epsilon portion of HBV were more active in inhibiting viral DNA levels than oligonucleotides targeted to other portions of the HBV sequence, including the S6, S7, S9, and S10 oligonucleotides cited by applicant as evidence that Korba's oligonucleotides do not work. It is noted that since the S6, S7, S9, and S10 oligonucleotides cited by applicant are disclosed to not have HBV inhibitory activity, this disclosure would serve as a further teaching towards the epsilon region as an antisense target site. It is further noted that the arguments concerning the activity of applicant's SEQ. ID. NO: 18 are not relevant to this rejection since

oligonucleotides targeted to this portion of the genome are not included in this rejection.

8. Claims 1, 8-16, 18, 20, 36, 48, and 49 stand rejected and claims 17, 19, 40-46, 50, 207-213, 215-222 and 224 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korba et al. as applied to claims 1, 8-14 , 36, 40-46, and 48-50 above, and further in view of Wu et al. (cited in the Office action mailed 5/28/96) or Wu et al. (designated B4 on the PTO-1449 submitted with the information disclosure statement filed 8/24/95), for the reasons set forth in the office action mailed 10/23/00.

Claims 1, 17 and 19 have been amended to recite oligonucleotides comprising SEQ. ID. NOS: 16 and 18, respectively. The change from closed transitional language (consisting of) to open transitional language (comprising) obviates the reasons for allowable subject matter set forth in the previous Office action and the claims are now rejected for the reasons of record (see rejection of these claims under 35 USC 102(b) as anticipated by Wu et al. set forth above). Claims 207-210, 211-213, and 216-222 limit the oligonucleotides of claims 16, 17 and 19 to being modified, to comprising one or more phosphorothioate internucleoside linkages, to comprising ribonucleotides and/or deoxyribonucleotides. Korba teaches that the anti-HBV oligonucleotides may be base on ribonucleotides or deoxyribonucleotides . Korba et al. further teach that the oligonucleotides may be modified and discloses phosphodiester, phosphorothioate or methylphosphonate linkages as examples of

modifications (col. 6, ln. 61, - col. 7, ln. 13). Claims 215 and 224 limit claims 16 and 19 to the oligonucleotides being included in a kit. It would be obvious to include the oligonucleotides in a kit for the reasons of record in the Office action mailed 10/23/00.

Applicant's arguments filed 3/21/01 have been fully considered but they are not persuasive. The rejection is traversed on the grounds that that Wu et al. disclose a single oligonucleotide and that there are no express or implied teachings in either Korba or Wu that would make it obvious to combine the references.

In response, it is submitted that Korba shows that the epsilon region of the HBV genome is an effective region for targeting antisense oligonucleotides relative to other regions of the HBV genome. See Korba, Table 1, and comments in the rejection of claims 1, 8-14 , 36, 40-46, and 48-50 above. Wu et al. demonstrate that the target region can be extended beyond the epsilon region to at least nucleotide no. 1923 of the HBV genome. It is noted that the target sites taught by Korba et al. and WU et al. are contiguous and overlap from nucleotides 1903 to 1908 of the HBV genome. One would, therefore, have a reasonable expectation that additional antisense oligonucleotides targeted to the combined target sites taught by Korba et al. and Wu et al. would have anti-HBV activity, and it would be a matter of routine experimentation to make and determine the activity of these additional oligonucleotides using the procedures disclosed by either of Korba or Wu. One would be motivated to do so to as a matter of routine optimization of the parameters

of antisense oligonucleotide target site selection and antisense oligonucleotide length.

9. Claims 1, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korba et al. in view of Uhlmann et al. (cited in the Office action mailed 5/28/96) for the reasons set forth in the office action mailed 10/23/00.

Applicant's arguments filed 3/21/01 have been fully considered but they are not persuasive. The rejection is traversed on the grounds that that Uhlmann does not remedy the deficiencies of Korba et al. However, as noted above, Korba et al. is not deficient. As noted in the previous Office action, it would have been obvious to combine the teachings to take advantage of the desirable properties that the Uhlmann teach that the incorporation of 2'-O-methyl ribonucleotides provide to antisense oligonucleotides, thereby improving the HBV antisense oligonucleotides taught by Korba et al.

10. Claims 1, 17, 19, 212, 214, 220, 221, and 223 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korba and either one of Wu et al, as applied to claims 1, 17, 19, 212, 220, and 221 above, and further in view of Uhlmann et al.

The claims are drawn to an antisense oligonucleotide which comprise SEQ. ID. NOS. 16 or 18, are complementary to a portion of the HBV epsilon region, which

inhibits HBV replication, and which comprises at least one ribonucleotide and at least one 2'-O-methyl nucleotide.

Both Wu et al. documents disclose an oligonucleotide targeted to nucleotides 1903-1923 of the HBV genome (Wu et al. (J. Biol. Chem.) p. 12436, col. 2, 2nd full ¶, lns. 11-15; Wu et al. (WO 93/04701), p. 10, ln. 8). This oligonucleotide comprises both SEQ. ID. NO: 16 (comprises nucleotides 1903-1922, see specification, Table 1) and SEQ. ID. NO: 18 (comprises nucleotides 1910-1921, see specification, Table 1). The Wu documents do not teach modified oligonucleotides.

Korba et al. teach oligonucleotides antisense to the epsilon region of HBV and which inhibit HBV replication (abstract, Figure 4, and Table 1). Korba teaches that these oligonucleotides may be base on ribonucleotides and may be modified (col. 6, ln. 61, - col. 7, ln. 13). Korba et al. do not specifically disclose a 2'-O-methyl modification or oligonucleotides comprising SEQ. ID. NOS: 16 and 18.

Uhlmann et al. describe the 2'-O-methyl modification of oligodeoxyribonucleotides and teaches that the modification confers the advantages of increased oligonucleotide stability and increased thermal stability of the oligonucleotide-target mRNA complex (p. 558, ¶ bridging cols. 1 and 2). Uhlmann does not teach an antisense oligonucleotide targeted to HBV.

It would have been obvious to the artisan of ordinary skill to combine the teachings of either Wu et al. document with those of Korba et al. and Uhlmann et al. to produce antisense oligonucleotides comprising SEQ. ID. NOS: 16 and 18, and

comprising 2'-O-methyl ribonucleotides. One would have been motivated to do so to increase the stability and target affinity of the oligonucleotides taught by Wu et al. One would have had a reasonable expectation of success because Uhlmann specifically teaches that incorporation of 2'-O-methyl ribonucleotides into antisense oligonucleotides is known to provide the oligonucleotides with these properties.

11. The following rejections are necessitated by newly found art.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13. Claims 1, 13, 40-46, 48, and 50 are rejected under 35 U.S.C. 102(e) as being anticipated by Carmichael (US Patent No. 5,728,518).

Claims 1 and 13 are drawn to an antisense oligonucleotide comprising SEQ. ID. NO: 12. Claims 40-46 limit the oligonucleotide of claim 1 to being a modified oligonucleotide, at least one phosphorothioate internucleoside linkage, and to comprising at least one deoxyribonucleotide or at least one ribonucleotide. Claim 50

is drawn to a composition comprising the oligonucleotide of claim 1 and a pharmaceutically acceptable carrier.

Carmichael discloses an antisense oligonucleotide targeted to the epsilon region of HBV that comprises SEQ. ID. NO: 12 (see Fig. 2, oligonucleotide designated "between", also SEQ. ID. NO: 7 disclosed by the '518 patent, and claim 18 of '518 patent). Carmichael teaches that the oligonucleotides can be RNA or DNA (col. 5, lns. 16-19) and may comprise modifications (col. 6, lns. 1-28) that include phosphorothioate internucleoside linkages (col. 6, lns. 6-13). Carmichael teaches compositions comprising the oligonucleotide and various pharmaceutically acceptable carriers (col. 6, ln. 29, to col. 9, ln. 38).

14. Claims 1, 12-15, 36, 40-46, and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carmichael (US Patent No. 5,728,518).

Claims 1, 12-15, and 36 are drawn to oligonucleotides comprising the sequences set forth in SEQ. ID. NOS: 11-14 and 45. Note the use of the open transitional language "comprising". Note also that these oligonucleotides are targeted to a region consisting of nucleotide positions 1858-1913 of HBV, as set forth in Table 1, p. 16 of the specification. Claims 40-46 limit the oligonucleotide of claim 1 to being a modified oligonucleotide, at least one phosphorothioate internucleoside linkage, and to comprising at least one deoxyribonucleotide or at least one ribonucleotide. Claims 48 and 49 are drawn to kits comprising one or

more oligonucleotides of claim 1. Claim 50 is drawn to a composition comprising the oligonucleotide of claim 1 and a pharmaceutically acceptable carrier.

Carmichael teaches a four different oligonucleotides directed to the region consisting of nucleotides 1850 to 1910 of the HBV genome (Fig. 2). These oligonucleotides 21 nucleotides in length and exhibit various levels of activity (Fig. 3, Example 1, starting col. 10, ln. 38, and Example 2, starting col. 12, ln. 14) with respect to reducing levels of HBV activity. Carmichael discloses an antisense oligonucleotide comprising SEQ. ID. NO: 12 (see Fig. 2, oligonucleotide designated "between"). Carmichael teaches that the length of the oligonucleotides can range from 15 to 32 bases in length with 20 to 25 bases preferred (col. 5, lns. 20-25). Carmichael teaches that the oligonucleotides can be RNA or DNA (col. 5, lns. 16-19) and may comprise modifications (col. 6, lns. 1-28) that include phosphorothioate internucleoside linkages (col. 6, lns. 6-13). Carmichael teaches compositions comprising the oligonucleotide and various pharmaceutically acceptable carriers (col. 6, ln. 29, to col. 9, ln. 38). Carmichael does not teach antisense oligonucleotides specifically comprising SEQ. ID. NOS: 11, 13, 14, or 45, and do not teach a kit comprising one or more oligonucleotides of claim 1.

It would have been obvious to the artisan of ordinary skill to develop additional oligonucleotides to the 1850 to 1910 target region of HBV. Because the target region is small (60 nucleotides) relative to the size of the sequences claimed (generally about 20 nucleotides) and Carmichael provides general guidance that

oligonucleotide length is preferred to be 20 to 25 nucleotides in length, the artisan would have at once envisaged oligonucleotides comprising the claimed sequences for testing. One would have been motivated to do so as a matter of routine experimentation to determine optimized antisense oligonucleotide sequences targeting this region. One would have had a reasonable expectation of success because Carmichael clearly shows that oligonucleotides targeted to different subsequences within the HBV epsilon target region have anti-HBV activity (Fig. 2).

Regarding the kit claims, it would have been further obvious to prepare the oligonucleotides for testing in the form of a kit to provide the benefits of convenience to the experimenter and to insure reproducibility by providing the oligonucleotide in a uniform format.

15. Claims 1, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carmichael (US Patent No. 5,728,518) as applied to claims 1 and 45 above, and further in view of Uhlmann et al.

The claims are drawn to are drawn to an antisense oligonucleotide comprising a sequence set forth in SEQ. ID. NOS: 11-14 or 45, which inhibits HBV replication and which comprises at least one 2'-O-methyl nucleotide. Carmichael is applied as above. Carmichael does not teach a 2'-O-methyl modified oligonucleotide.

Uhlmann et al. describe the 2'-O-methyl modification of oligodeoxyribonucleotides and teaches that the modification confers the advantages of increased oligonucleotide stability and increased thermal stability of the oligonucleotide-target mRNA complex (p. 558, ¶ bridging cols. 1 and 2). Uhlmann does not teach an antisense oligonucleotide targeted to HBV.

It would have been obvious to the artisan of ordinary skill to combine the teachings of Carmichael and Uhlmann et al. to produce antisense oligonucleotides targeted to the epsilon region of HBV and comprising 2'-O-methyl ribonucleotides. One would have been motivated to do so to increase the stability and target affinity of the oligonucleotides taught by Carmichael. One would have had a reasonable expectation of success because Uhlmann specifically teaches that incorporation of 2'-O-methyl ribonucleotides into antisense oligonucleotides is known to provide the oligonucleotides with these properties.

16. Claims 1, 8-20, 36, 40-46, 48-50, 207-213, 215-222, and 214 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carmichael (US Patent No. 5,728,518) taken together with Korba et al. (US Patent No. 5,646,262), Wu et al. (cited in the Office action mailed 5/28/96) and Wu et al. (designated B4 on the PTO-1449 submitted with the information disclosure statement filed 8/24/95)

Claims 1, 8-20, and 36 are drawn to oligonucleotides comprising the sequences set forth in SEQ. ID. NOS: 7-19 and 45. Note the use of the open

transitional language "comprising". Note also that these oligonucleotides are targeted to a region consisting of nucleotide positions 1829-1929 of HBV, as set forth in Table 1, p. 16 of the specification. Claims 40-46, 207-213, and 216-222 limit the oligonucleotide of claims 1, 16, 17 and 19 to being a modified oligonucleotide with at least one phosphorothioate internucleoside linkage, and to comprising at least one deoxyribonucleotide or at least one ribonucleotide. Claims 48, 49, 215, and 224 are drawn to kits comprising one or more oligonucleotides of claims 1, 17, and 19. Claim 50 is drawn to a composition comprising the oligonucleotide of claim 1 and a pharmaceutically acceptable carrier.

Carmichael is applied to claims 1, 12-15, 36, 40-46, and 48-50 above. Carmichael does not teach oligonucleotides targeted to a region of HBV other than the region defined by nucleotides 1850-1910.

Korba et al. teach a large number of different oligonucleotides directed to the region consisting of nucleotides 1841 to 1908 of the HBV genome (oligonucleotide L1e starts at 1841 while L2d starts at 1887 (col. 13, lns. 22-39) to end at 1908). These oligonucleotides have various lengths and exhibit various levels of activity (Fig. 4 and Table 1) with respect to reducing levels of HBV. Korba et al. provide general guidance that oligonucleotide length is preferred to be 14 to 25 nucleotides in length (col. 7, lns. 46-48), and that internucleoside linkages can be modified to improve stability with phosphorothioate being cited as an example of such a modification (col. 7, lns. 6-14). Korba et al. do not teach antisense oligonucleotides

comprising sequences outside the 1841 to 1908 target region set forth in the claims. Korba et al. also do not teach a kit comprising one or more oligonucleotides of claims 1, 17 or 19.

Both Wu et al. documents teach an oligonucleotide targeted to nucleotides 1903-1923 of HBV (Wu et al. (J. Biol. Chem.) p. 12436, col. 2, 2nd full ¶, lns. 11-15; Wu et al. (WO 93/04701), p. 10, ln. 8). This oligonucleotide comprises SEQ. ID. NOS: 16 and 18 (claims 17 and 19). Wu et al teach that this oligonucleotide produces a reduction in HBV surface antigen (Wu et al. (J. Biol. Chem.) abstract, lns 9-14; Wu et al. (WO 93/04701), Fig. 2). Neither Wu et al. document teaches an antisense oligonucleotide targeted outside of nucleotides 1903-1923 of HBV.
It would have been obvious to the artisan of ordinary skill to combine the teachings of Carmichael, Korba et al. and those of either Wu et al. reference to extend the HBV antisense target region from the region bounded by nucleotides encompass nucleotides 1841 to 1923. One would have been motivated to do so to find additional optimized antisense oligonucleotides for inhibiting HBV, more particularly those that can reduce HBV antigen levels. As noted above, because the target region is small (82 nucleotides) relative to the size of the sequences claimed (generally about 20 nucleotides). Korba et al. provide general guidance that oligonucleotide length is preferred to be 14 to 25 nucleotides in length, and Carmichael provides general guidance that oligonucleotide length is preferred to be

20 to 25 nucleotides in length. Therefore, the artisan would have at once envisaged oligonucleotides comprising the claimed sequences for testing.

One would have had a reasonable expectation of success because the antisense target sites taught by Carmichael and Korba et al. overlap from HBV nucleotides 1850-1903, are contiguous with the target sequence taught by Wu et al, and overlap with the sequence taught by Wu et al. from HBV nucleotides 1903 to 1910. One would, therefore, have a reasonable expectation that additional antisense oligonucleotides targeted to the combined target sites taught by Carmichael, Korba et al. and Wu et al. would have anti-HBV activity, and it would be a matter of routine experimentation to make and determine the activity of these additional oligonucleotides using the assays disclosed by any one of Carmichael, Korba et al. or Wu et al.

Regarding the kit claims, it would have been further obvious to prepare the oligonucleotides for testing in the form of a kit to provide the benefits of convenience to the experimenter and to insure reproducibility by providing the oligonucleotide in a uniform format.

17. Claims 1, 17, 19, 45, 47, 212, 214, 220, 221, and 223 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carmichael taken together with Korba et al. and either one of Wu et al, as applied to claims 1, 17, 19, 45, 212, 220, and 221 above, and further in view of Uhlmann et al.

The claims are drawn to an antisense oligonucleotide which comprise SEQ. ID. NOS. 7-19 and 45, which inhibits HBV replication, and which comprises at least one 2'-O-methyl nucleotide.

Each of Carmichael, Korba et al. and Wu et al. are applied as in the rejection of claims 1, 17, 19, 45, 212, 220, and 221 above. These references do not teach anti-HBV antisense oligonucleotides comprising 2'-O-methyl modifications.

Uhlmann et al. describe the 2'-O-methyl modification of oligodeoxyribonucleotides and teaches that the modification confers the advantages of increased oligonucleotide stability and increased thermal stability of the oligonucleotide-target mRNA complex (p. 558, ¶ bridging cols. 1 and 2). Uhlmann does not teach an antisense oligonucleotide targeted to HBV.

It would have been obvious to the artisan of ordinary skill to combine the teachings of Carmichael, Korba et al. and Wu et al. with those of Uhlmann et al. to produce antisense oligonucleotides targeted to the epsilon region of HBV and comprising 2'-O-methyl ribonucleotides. One would have been motivated to do so to increase the stability and target affinity of the oligonucleotides taught by Carmichael, Korba et al. and Wu et al. One would have had a reasonable expectation of success because Uhlmann specifically teaches that incorporation of 2'-O-methyl ribonucleotides into antisense oligonucleotides is known to provide the oligonucleotides with these properties.

18. No claim is allowed.

19. Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The FAX numbers are (703) 308-4242 and (703) 308-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Unofficial papers, such as draft responses, may be transmitted to the examiner directly at (703) 305-7939. It is recommended that the examiner be notified when a fax is sent to this number.

Any inquiry concerning this communication or earlier communications should be directed to Thom Larson, whose telephone number is (703) 308-7309. The examiner normally can be reached Monday through Friday from 9:00 AM to 5:30 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

Thomas G. Larson, Ph.D.
Examiner

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600